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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

San Juan District
Compliance Branch
466 Fernandez Juncos Ave.
San Juan, Puerto Rico 00901
Telephone: 787-474-9500
FAX: 787-729-6658

December 20, 2004

WARNING LETTER
SJN-05-02

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Severo Pina
Chief Executive Officer
Respi Care Group of Puerto Rico
PMB 367
200 Ave. R. Cordero-Suite 140
Caguas, PR 00725-3757

Dear Mr. Pina:

On June 9-17, 2004, the Food and Drug Administration (FDA) conducted an inspection of your facility located at Luis Muñoz Rivera Ave. V-23, Urb. Mariolga, Caguas, PR 00725. Our Investigator, accompanied at the end of the inspection by a representative from the Puerto Rico Health Department (PRHD), Drugs, and Pharmacy Division, documented serious violations of the Federal Food, Drug, and Cosmetic Act (Act). The inhalation solution products manufactured by your firm are defined as drugs within the meaning of Section 201(g) of the Act, and are unapproved new drugs under Section 505. They are also adulterated within the meaning of Sections 501(a)(2)(B) and 501(c) of the Act and misbranded within the meaning of Section 502(f)(1).

As you may be aware, Section 127 of the FDA Modernization Act of 1997 amended the Act by adding section 503A, which specified certain conditions under which compounded human drugs could be exempt from certain requirements of the Act. In April 2002, however, the United States Supreme Court struck down the commercial speech restrictions in section 503A of the Act as unconstitutional. Accordingly, all of section 503A is now invalid.

As a result, the agency now utilizes its longstanding policy of exercising its enforcement discretion regarding certain types of pharmacy compounding. This policy is articulated in Compliance Policy Guide (CPG), section 460.200, issued on June 7, 2002. The CPG contains factors that the agency considers in deciding whether to exercise enforcement discretion. One factor that the agency considers is whether a compounded product is a copy of a commercially available product and, if so, whether there is any documentation of a medical need for the compounded product.

On July 29, 2004, we received the letter you sent in response to the FDA 483 that our investigators issued at the close of the inspection. In your letter, you purport to be a compounding pharmacy. However, our investigation finds that your firm has transcended the practices associated with traditional extemporaneous compounding and that your operation is more akin to that of a drug manufacturer.

The products produced by your firm, albuterol sulfate and budesonide inhalation solutions, are sold in the same strength as the commercially available products. We acknowledge that your compounded budesonide medication is supplied in [redacted] and the commercially available product is supplied in [redacted] but we do not view the availability of [redacted] dose vials as a meaningful distinction and your firm's records fail to document a patient-specific medical need for the compounded solution.

Furthermore, since the start of your firm's operation in 2002, you have produced [redacted] batches of inhalation solutions such as albuterol, ipratropium, budesonide, and combinations of these ingredients. According to a report provided by your firm, during a one year period (from 6/17/03 to 6/17/04), you dispensed [redacted] vials (unit-dose vials) of albuterol, ipratropium, budesonide, and combinations of these ingredients, with an average of [redacted] vials dispensed per month. During a one month period (5/10/04 to 6/10/04), your firm manufactured [redacted] lots of drug products that were distributed in [redacted] and [redacted] vials. This equates to approximately, [redacted] vials, or [redacted] vials, or [redacted] vials. These drugs were distributed to patients in Puerto Rico and Florida. We do not believe that such production volume is consistent with that of a pharmacy that is engaged in the traditional practice of extemporaneous pharmacy compounding. We are especially convinced of this in this instance, given that most of the drugs you have produced in these volumes are essentially copies of commercially available, FDA-approved drugs.

In addition, the Puerto Rico Department of Health (PRDH) embargoed [redacted] units of [redacted] different inhalation solution formulations because your firm's operations were not in conformance with the applicable laws of Puerto Rico. Furthermore, even though your available inventory was embargoed by PRDH officials on June 17, 2004, your firm continues to manufacture and distribute drug products with virtually no regard to the current good manufacturing practice (cGMP) requirements in the Act and the cGMP regulations set forth in the Code of Federal Regulations, Title 21, Parts 210 and 211 (21 CFR Part 210 and 211).

In light of the above, your firm is in violation of the following sections of Act:

Section 505(a)
The inhalation solutions manufactured by your firm are drugs within the meaning of Section 201(g) and new drugs within the meaning of section 201(p) of the Act. Accordingly, they may not be introduced or delivered for introduction into interstate commerce under Section 505(a) of the Act since they are not the subject of FDA-approved drug applications.

Section 502(f)(1)
Your products are misbranded under Section 502(f)(1) of the Act in that their labeling fails to bear adequate directions for use and they are not exempt from this requirement under 21 CFR § 210.116 since adequate directions for use are not known to the common individual.

Section 502(o)
Your drug products are misbranded under Section 502(o) of the Act because they are manufactured in an establishment not duly registered under Section 510 of the Act, and they have not been listed as required by Section 510(j). Your facility is not exempt from registration and drug listing under 21 CFR § 207.10 and Section 510(g) of the Act since it is engaged in the manufacture and distribution of drugs.

Section 501(a)(2)(B)
Your drug products are adulterated within the meaning of Section 501(a)(2)(B) of the Act in that the methods, controls, and procedures used in the manufacture, processing, packing, and holding do not conform to Current Good Manufacturing Practice (CGMP) regulations set forth in 21 CFR Parts 210 and 211. These products are also adulterated within the meaning of Section 501(c) of the Act in that you are manufacturing drug products that are not recognized by an official compendium and the strength of the products differs from the label claim on the unit doses' primary labeling.

Deviations from these regulations include, but are not limited to, the following:

1. Failure to establish and follow appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile. Such procedures include validation of any sterilization processes [21 CFR § 211.113(b)].

   Specifically, you have not validated the aseptic filling operations in that media fills are not performed to assess your aseptic technique. Additionally, you have not documented that the sterilization cycles, identified in your firm's SOP [redacted], actually achieve sterility, as your firm lacks demonstration of a [redacted] or better sterility assurance level for your sterilization process.

Furthermore, you have not performed any qualification studies on your steam sterilizer, such as temperature distribution studies or heat penetration studies utilizing established sterilizer load patterns. Your firm uses the sterilizer to sterilize items such as the manifold to the filling equipment, clamps and glass beakers.

During the inspection we observed that you did not sterilize the plastic components utilized in your filling processes, such as the filter holders and transfer tubing, which make contact with the drug product. You stated that these components could not be sterilized because the plastic could not withstand the high temperatures in the sterilization cycles. Please explain how you assure the sterility of these plastic parts.

Regarding gowning, employees at your firm do not perform aseptic gowning techniques. Gowning should provide a barrier between the body and exposed sterilized materials and prevent contamination from particles generated by, and microorganisms shed from, the body. During manufacturing of drug product, your employees were observed wearing gowns that did not fully cover hair and skin, donning jewelry, and wearing hair covers that did not fully cover employees' heads to the hair line. Shoe covers were not worn by some of the employees. Also, employees were observed entering/exiting an "unclassified" storage area through an egress in the "clean room." Your gowning procedure SOP [redacted] is inadequate, in that it does not describe aseptic gowning technique. Instead, the SOP is comprised of two instructions that inform the employee of the types of covering (hair, feet, gown, mask, etc.) that must be worn in the "clean room" and advises the employee to follow "compounding and/or filling process personal aseptic techniques..."

We acknowledge your response, dated July 23, 2004, which states that your firm is in the process of substantially upgrading its procedures to prevent microbial contamination and that your firm is committed to achieving compliance with USP <797>. Please be advised that drug manufacturers are required to comply with the CGMPs as stated in 21 CFR Parts 210 and 211 and that 21 CFR § 200.51 requires that all aqueous based solutions for oral inhalation be manufactured to be sterile.

2. Failure to have control systems for the firm's operations necessary to prevent contamination of drug product during aseptic processing [21 CFR § 211.42(c)(10)]. Specifically, the aseptic processing area, used in the manufacture of a drug product, does not have suitable construction to facilitate cleaning, maintenance, and proper operations. For example, the walls consist of a painted drywall only, there is chipped and peeling paint on the walls, items such as clipboards with paper are hung from the wall, the ceiling consists of fibrous ceiling tiles mounted within a "drop ceiling" frame, ceiling lighting fixtures are not appropriately designed, lighting fixtures over benches are hung in a manner that propagates collection of dust particles, and floors are constructed of tile and grout. The design features of the aseptic processing area are not smooth, hard surfaces that facilitate cleaning and sanitization. Additionally, cleaning and disinfecting within this area is inadequate, as evidenced by visibly dusty shelves and working surfaces.

You stated during the inspection of your firm that the aseptic area was classified as a Class 100 (ISO Class 5) clean room. The investigator noted that the room adjacent to the aseptic area is an unclassified area utilized by ungowned personnel performing "prescription data entry." The only entrance into the aseptic area is through a door in the unclassified room. The areas immediately adjacent to the aseptic processing area, at a minimum, should meet Class 10,000 (ISO 7) standards under dynamic conditions. In addition, the wall separating the two areas is only a drywall partition that does not extend to the structural ceiling of the room. The "drop ceiling" in the unclassified area extends over the partition into the aseptic area. Thus, there is no control of room pressurization to ensure that the aseptic area will maintain significant positive pressure relative to the unclassified area when employees enter/exit the aseptic area.

Finally, our inspection disclosed that you perform environmental monitoring only on a semi-annual basis. You have also not established any written procedures for environmental monitoring that specifically address issues such as sample location, sample frequency, sampling technique, sample size, analytical techniques, interpretation of results, and corrective actions in the event of failures.

We acknowledge your response, dated July 23, 2004, in which your firm promises facility upgrades such as replacing tile floor with PVC, caulking lighting fixtures and air conditioning ducts, purchasing a particulate counter to check the clean room, regularly changing the pre-filters for the HVAC system, and testing the aseptic area and HEPA filters for bacterial contamination. These changes do not adequately address all CGMP concerns, as delineated above, with respect to your aseptic processing area.

3. Failure to assure conformance to sterility requirements for each batch of drug product purporting to be sterile [21 CFR § 211.167(a)]. Specifically, your firm failed to assure that each batch of your aqueous based drug products for oral inhalation are free of any objectionable microorganisms. Since February 2002, only [redacted] batches of aqueous based drug product for oral inhalation were tested for sterility. During this time frame you have manufactured approximately [redacted] batches of inhalation solutions containing Albuterol Sulfate, Ipratropium Bromide, Budesonide, and Dexamethasone. Additionally, the eight batches were not tested in accordance with USP General Chapter <71>, "Sterility Testing". USP <71> states that the minimum incubation period for sterility samples is 14 days, yet your firm only incubated samples for 7 days.

We acknowledge your response, dated July 23, 2004, where you state that 40 batches (as opposed to [redacted] batches) have been submitted for sterility testing. This number still does not satisfy 21 CFR § 211.167(a), which states that each batch must be tested.

4. Failure to assure, through appropriate laboratory determination, that each batch of drug product conforms to its final specifications [21 CFR § 211.165]. Specifically, since February 2002 you have tested only [redacted] out of approximately [redacted] manufactured lots for conformance with final specifications (i.e., specifications other than sterility).

   We acknowledge your response, dated July 23, 2004, where you state that 40 batches have been submitted for identity testing. This number still does not satisfy 21 CFR § 211.165, which states that each batch must be tested.

5. Failure to establish the reliability of a supplier's analyses of drug components through validation of the supplier's test results and to perform at least one specific identity test on the components received from the supplier [21 CFR § 211.84(d)(2)]. When our investigator requested the certificates of analysis for the components used to manufacture a batch on May 21, 2004 (Batch # [redacted], you provided certificates that were dated June 09, 2004 for Albuterol Sulfate solution (Lot # [redacted] and Ipratropium Bromide solution (Lot # [redacted]. Further evaluation of the batch record revealed that the Albuterol Sulfate solution used in the manufacturing of batch # [redacted] was Lot # [redacted] (and not Lot # [redacted]. Finally, you have not verified the reliability of the supplier's analyses through any validation of the supplier's test results. Since February 26, 2002, you have manufactured approximately [redacted] million vials of the [redacted] different formulations of drug product utilizing these components. In addition, you have not conducted an identity test on any incoming components.

   Your response dated July 23, 2004, does not address the Agency's concerns regarding the testing of components used to manufacture aqueous based solutions for oral inhalation.

6. Failure to establish a written testing program designed to assess the stability characteristics of drug products [21 CFR § 211.166]. Specifically, your firm does not have data to justify the assigned expiration date of 90 days at room temperature for each drug product. Only two formulations out of the [redacted] different aqueous based solutions for inhalation that you manufacture were placed on stability to determine an appropriate expiration dating period. The expiration dating period determined from these studies was applied unilaterally to all [redacted] formulations of your drug products.

   You also have not performed any preservative effective testing to determine whether benzalkonium chloride effectively inhibits microbial growth in your drug products through their expiration dating period. This preservative is used in the manufacture of almost all of your drug products.
   In your response dated July 23, 2004, you state that the investigator only requested a copy of one stability study report. However, during the

inspection, when the investigator specifically asked for evidence to justify the expiration date for your products, you only provided stability studies for two out of the [redacted] different formulations of aqueous based solutions for oral inhalation that you manufacture. You also stated that these studies represented a "worst-case scenario" for the stability of your drug products. However, your firm had no scientific rationale or data to prove that the two products tested in stability represented a worst-case scenario or are representative of the stability of your other products. Be advised that as per 21 CFR § 211.166 of the CGMPs, manufacturers are required to assess the stability of each drug product that they manufacture. Your response also does not state how you determine that benzalkonium chloride effectively inhibits microbial growth in your drug products through the expiration dating period.

7. Failure to establish written procedures for production and process control designed to assure that drug products have the identity, strength, quality and purity they purport to possess [21 CFR § 211.100(a)]. Specifically, you do not have any procedures or controls to determine that each batch of drug product contains an effective level of the preservative benzalkonium chloride.

   Additionally, you do not have any procedures or controls describing the mixing of Budesonide with Ethyl Alcohol [redacted] to increase its water solubility. On its own, Budesonide is not soluble in water. The Budesonide/Ethyl Alcohol solution is further mixed with water soluble components such as Albuterol Sulfate and Ipratropium Bromide to manufacture the final drug product. Also, you do not have any written procedures for controlling the storage conditions of Budesonide components. Budesonide is extremely sensitive to light, yet the in-process batches of Budesonide/Ethyl Alcohol solution were stored in clear beakers that were partially covered with a [redacted] type covering. The beakers were stored in a refrigerator with a transparent glass door, within the manufacturing area.

   We acknowledge your response, dated July 23, 2004, which stated that the storage conditions of Budesonide components would be improved. However, the response does not clarify how you will determine whether each lot of drug product contains an effective level of benzalkonium chloride.

8. Failure to clean, maintain and sanitize equipment at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug product [21 CFR § 211.67(a)]. Specifically, your firm's SOP [redacted] states that isopropyl alcohol [redacted], and [redacted] shall be used to disinfect equipment, and that these cleaning agents will be rotated on a regular basis. However, you have not determined whether your cleaning cycle adequately removes the cleaning agents from equipment product contact surfaces, nor have you determined whether your cleaning agents effectively remove product residue from equipment product contact surfaces. The investigator noted that consecutive lots of different drug products of varying concentrations are manufactured on common equipment.

We acknowledge your response, dated July 23, 2004, which states that your firm has established dedicated equipment for water soluble products and water insoluble products. Please explain how you intend to prevent cross-contamination in the production of drug products that contain different water soluble components, such as albuterol sulfate and ipratropium bromide.

9. Failure to establish and follow written cleaning procedures for the cleaning of equipment used in the manufacture, processing, packing, and holding of drug products [21 CFR § 211.67(b)]. Specifically, your firm's SOP[redacted]" does not identify a specific cleaning or maintenance schedule for the manufacturing equipment. The SOP only states that the pharmacy will be cleaned on a "routine basis" and that a "major sanitation cleaning" will be performed on a weekly basis. Furthermore, there are no other procedures which sufficiently address various aspects of a cleaning program such as: assignment of responsibility for the cleaning and maintenance of equipment; the methods, equipment and materials used in the cleaning operations; the protection of cleaned equipment and the inspection for cleanliness in equipment prior to use.

10. Failure to include in each batch record complete information relating to the production and control of each batch and document each significant step in the manufacturing, processing, packing or holding of each batch [21 CFR § 211.188(b)]. Specifically, you do not record the amount of active ingredients, excipients, and other ingredients weighed and added during the manufacturing of your finished products in the batch record. Additionally, your batch record does not state each step performed during the production of a batch. It also fails to identify the persons performing and directly supervising each step.

    We acknowledge your response, dated July 23, 2004, which states that your firm has committed to revising its procedures, policy, and practices regarding developing, executing and verifying batch record information. However, your response does not address the requirement in 21 CFR § 211.188(b) to document each significant step in the production of your batch. Please revise your procedures accordingly.

11. Failure to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures to assure that drug products conform to the appropriate standards of identity, strength, quality, and purity [21 CFR § 211.160(b)]. Specifically, the certificates of analysis for multiple lots containing Albuterol Sulfate, Ipratropium Bromide and Budesonide aqueous based solutions reference a USP XXV method for the identity tests for these drug products. Inspection of USP XXV revealed that a USP monograph does not exist for any of these aqueous based solutions for oral inhalation.

We acknowledge your response, dated July 23, 2004, which states that the testing of final drug product is outsourced to your contracted services laboratory and that your contractor is "registered with the FDA, is ISO-certified and is affiliated with the American Society of Quality (ASQ)." However, in light of your contractor referencing a USP method that does not exist in the compendium, you have provided no further assurance that the specifications, standards, and testing procedures used to test your drug product have been scientifically established.

12. Failure to have a quality control unit that has the responsibility and authority to approve or reject all components, in-process materials, drug products, and all procedures or specifications impacting on the identity, strength, quality, and purity of the drug products [21 CFR § 211.22]. All of the above deficiencies are indicative of your Quality Control Unit's inability to meet the requirements impacting the identity, strength, quality, and purity of your drug products.

    Finally, we collected and analyzed samples from Lot #'s [redacted] and [redacted] of your aqueous based solutions for oral inhalation. These lots have been distributed. For Lot # [redacted], Ipratropium Bromide Premixed Solution 0.02%, we noted that the label claim on the unit dose label differed from the label claim on the plastic pack containing unit dose vials. Our assay, which was based on the primary label located on each unit dose, revealed that the drug product contained [redacted] of the label claim for Ipratropium Bromide. Similarly, for Lot # [redacted] Albuterol Premixed Solution [redacted] we noted that the unit dose vials and the exterior packaging had different label claims. Our assay, which was based on the primary label located on each unit dose, revealed the drug product contained [redacted] of the label claim for Albuterol Sulfate. Lot # [redacted] Albuterol/Ipratropium/Budesonide solution [redacted] did not have labels on each unit dose that stated the concentration of active ingredients in solution. Our assay relied on the label claim that was located on the plastic pack containing unit dose vials. Our assay revealed that the drug product contained [redacted] of the label claim for Albuterol Sulfate. During the inspection, we observed that you sent only eight lots of final drug product for identity testing; the Lot Numbers stated above were not part of this group. The certificates of analysis for the eight lots revealed that your firm uses an acceptance criteria for the final product assay of "not less than [redacted] and not more than [redacted]" of the label claim for your aqueous based solutions for oral inhalation. Based upon our analysis, we have determined that these drug products are adulterated under Section 501(c) of the Act. We request that you reply within 10 days of your receipt of this letter stating the actions you will take to address these adulterated drug product lots that are currently in distribution.

    In summary, the above violations are not intended to be an all-inclusive list of deficiencies at your facility and may not be limited to the above mentioned products. It is your responsibility to ensure adherence to each requirement of the Act and the cGMP regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts. We are

aware that you continue to manufacture and distribute adulterated aqueous based solutions for oral inhalation which are required by the regulations to be sterile. Based on the observations issued in this Warning Letter, there is no assurance of the sterility, quality, or safety of your drug product.

Please reply within 15 days of your receipt of this letter stating the action you will take to bring your drug products into compliance and to address the products that are currently on the market and within their expiration period. If corrective actions can not be completed within 15 working days, state the reason for delay and the time within which corrections will be complete.

You should take prompt action to permanently correct these deviations and prevent their recurrence. Failure to do so may result in regulatory action without further notice including seizure and/or injunction.

Your reply should be sent to the Food & Drug Administration, San Juan District Office, 466 Fernandez Juncos Ave., San Juan, PR 00901-3223, Attention: Miguel A. Hernandez, Compliance Officer.

Sincerely,

Donald J Voeller
District Director

Enclosure